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THE DUCTLESS GLANDS.

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EXCEPT it be in the kingdom of the antitoxins, there is no therapeutic realm in which, during the last two or three years, so much of interesting discussion and experiment has been going on as in that of the ductless glands. The first surprising discovery of the value of the thyroid body in practical medicine has been so far confirmed and corrected by continuing experience that as a drug the gland rests upon a firm foundation of knowledge. We now know that it is a very useful remedy in the treatment of myxœdema; that it is often of great service in those forms of obesity in which there is a tendency to general softness and flabbiness of tissue and to lack of proper development of the blood; in other words, in the so-called "fat anæmics" of some writers. In insanity the records are, on the whole, records of failure rather than of success, and though in some instances of melancholia and other chronic insanities good is alleged to have been achieved, in general little is to be expected; if in any case of insanity the practitioner determines to essay the use of the thyroid extract, it is essential that the bodily weight be carefully watched and that the remedy be suspended the moment it begins distinctly to fall or cardiac weakness and rapidity of heart-action or breathlessness develop. In skin-diseases good results have been sometimes achieved, especially in cases in which there is large development of tissue of a low type, as in keloid, hypertrophied cicatrix, and sometimes in chronic eczema with great thickening of tissue; but here, again, the drug often fails us.

A very important observation is that of Dr. R. Lépine, who has reported a case of progressive myopathy in which the subject, a day-laborer, came into the hospital entirely incapacitated for work by the widespread muscular change. About 900 grains a day of the fresh thyroid gland were given him for a number of weeks; at the end of that time the improvement had been so great that the man refused to stay longer in the hospital, asserting that he was entirely able to do his work. It was noted that those muscles which had undergone complete change did not seem to be distinctly affected, but that the process appeared to have been arrested and great improvement to have taken place in the fibres of those muscles which were in the incipiency of change. It seems also well established that in the true goitre of Switzerland and other mountain countries, if the thyroid be given before calcareous degeneration has taken place, it will bring about absorption of the overgrown gland—a result which strongly contrasts with the fact that the thyroid extract usually greatly aggravates the symptoms of exophthalmic goitre, in which disease it has marked capabilities for harm rather than for good.

The loss of weight which is so often produced by the ingestion of thyroid gland or its preparations strongly indicates that that body increases tissue-waste; and the early experiments of Mendel, of Napier, of Ord, and others were concordant in showing that there is under the influence of the thyroid extract an increase in the output of urea. It is true that Vermehren affirms that this increase occurs only in myxœdematous subjects and in those of advanced age, no young people in his experiments having been affected; whilst Paul Mayer failed to get any evidence of increased nitrogenous waste after the exhibition of thyroidin. On the other hand, however, Bleibtren and Vendelstadt found in an individual case that one-sixth part of the loss of weight could be accounted for by the increased elimination of nitrogenous material, while the other five-sixths was the result of the destruction of the fat and other carbohydrates; while Irsai, Vas, and Gara, in several goitrous individuals, determined that the loss of weight was accompanied by an increase in the elimination of nitrogen, phosphorus, sodium chloride, and uric acid; and in the experiments upon dogs Roos, Burger, Scholz, and Treupel have all noticed pronounced and continuing increase in the elimination of nitrogen and of phosphorus. Curiously, the elimination of chlorine has usually been at first increased, afterward lessened.

These various researches are sufficient in extent to warrant a definite conclusion, and it would appear, therefore, that the thyroid and its preparations lessen the bodily weight in part by causing a destruction of the nitrogenous tissues, but still more largely by wasting the carbohydrates of the body.

The question as to the nature of the active principle of the thyroid body is at present one of very great interest, to which a partial answer can be given.

In 1895 Baumann announced that the physiological activity of the thyroid gland depended upon the presence of a proteid substance containing iodine, to which he gave the name of thyroiodin; a year later Gottlieb found in a series of experiments that while he could maintain the life of dogs which had suffered thyroidectomy by feeding them on the thyroid gland or giving them thyroid extract, the thyroiodin was incapable of preserving the animal's existence. The contrary result, however, reached in the experiments of Hildebrandt and of Notkin, confirmed by the experimental and clinical evidence gathered together by E. Roos, Arthur Hennig, Treubel, Ewald, Levy, and others, confirm the statements of Baumann and seem to prove that the thyroiodin is the chief active principle of the thyroid body; but that while it is capable of saving the life after thyroidectomy, it does not put an end to the tetanoid symptoms which are often so prominent in the dog after removal of the gland, and that therefore there must be in the thyroid body some second active substance. It is possible that this second substance is the thyreo-antitoxin of Fränkel, although there is at present no proof of this, and the researches of Robert Hutchison would seem to indicate that thyreo-antitoxin is inert.

In regard to the method of administration, thyroiodin is scarcely a commercial product. Thyroidin of Merck's *Index* and of the German writers is nothing more than the dried thyroid gland of the ox. It certainly is efficient, and, as the dose is only 5 grains, can be used in capsules, three to five doses in the twenty-four hours. If in any case the symptoms of thyroidism—*i. e.*, nervousness, shortness of breath, rapid pulse, or other physiological symptoms—appear, the daily dose should be reduced.

THYMUS GLAND. Concerning the medical value of the *thymus gland* we have little or no knowledge, except that the first statements as to its value in exophthalmic goitre have not been borne out by more recent clinical studies, as was especially shown by Mr. Hector Mackenzie in the elaborate paper published in this JOURNAL not long since.

PITUITARY BODIES. The fact that the *pituitary body* is often diseased in cases of acromegaly naturally suggests that it belongs to the ductless glands and has widespread relations to the general nutrition which might be availed of in the treatment of disease. On the other hand, however, so many cases of acromegaly without recognizable disease of the pituitary gland, and so many cases of disease of the pituitary gland without acromegaly, have been reported, that at present it is very doubtful whether the connection between this body and acromegaly is ever anything more than an accidental coincidence. There is at present no clinical evidence that the pituitary body has therapeutic value; but it is interesting to note that the experiments of Oliver and Schäfer indicate that there is similarity or resemblance of function between it and the suprarenal capsules, at least in so far that its extract, when given intravenously to the dog, like that of the suprarenal capsule, produces a rise of the blood-pressure, which Oliver and Schäfer believe that they have shown to be the outcome of contraction of the arterioles.

SUPRARENAL CAPSULES. During the last year or two much work has been performed for the determination of the function of the suprarenal capsules and of their possible use in therapeutics. It is not yet settled whether or not they contain a true active principle, much less what that active principle is. They certainly contain some toxic substance, but the question now pressing for solution is: Is this toxic principle produced by the gland or is it only filtered, as it were, out of the blood and accumulated in the gland?

It seems established that the adrenal bodies contain a considerable amount of neurin, and that this substance appears in the urine of patients suffering from Addison's disease. Two views not necessarily antagonistic or incompatible have been held about this matter; one that of Marino-Zuco and Guaruceri, that the active toxic agent of the gland is neurin; the other that of Albanèse, who believes that the function of the gland is to destroy or overcome the poisonous effects of neurin. The latter view has been especially combated by E. Boinet, but is not improbable.

The theory of the English physiologists Oliver and Schäfer is that the glands produce a substance which maintains muscular tonus, while that of E. Dubois, resembling that of Albanèse, is that they destroy toxic principles originating in the body, especially those resulting from muscular work. At present the theory that the chief function of the adrenals is to destroy poisonous principles produced in the economy seems the most probable, since it receives confirmation from the experiments of Boinet, that the muscles, blood, etc., of rats from which the capsules have been exsected contain a toxic substance, as well as from the discoveries of Charrin and Langlois that the suprarenal capsule triturated with nicotine lessens its poisonous power; and that injections of the capsule diminish the action of atropine in the living dog. The activity of the capsules is lessened or altogether destroyed by disease, the swollen, inflamed capsule of diphtheria being entirely inert. According to Langlois, there is a direct relation between the activity of a suprarenal capsule and its power to strike a blue color with the perchloride of iron.

The intravenous injection of minute doses of the suprarenal capsule is followed in the dog by a great rise of blood-pressure, which the experiments of Oliver and Schäfer apparently prove to be due to a contraction of the arterioles, caused by a direct action of the poison upon their muscular coats. Using the oncometer or plethysmograph, they found that there was always a contraction of the limb, the spleen, the kidney, or other organ enclosed, amounting from 20 to 25 per cent., directly after the intravenous injection of the extract; the contraction being entirely independent of the nervous system. The rise of pressure was accompanied by slowing of the heart-action, which was due to a stimulation of the vagi, believed to be centric, and was prevented by previous use of atropine or by section of the vagi. It would appear also, from these experiments, as though the heart itself was markedly energized by the extract, since the rise of the blood-pressure after section of the vagi—that is, after putting aside the stimulation of the inhibitory apparatus of the heart by the extract—was often double what it had been during the period of slow cardiac action.

Although the reputation of Schäfer makes it exceedingly improbable that there is any inaccuracy in his work, it must be acknowledged that there is distinct contradiction as to fact between the English and Polish physiologists. Szymonowicz and Cybulski affirm, first, that after section of the cord the extract is incapable of producing rise of blood-pressure; second, that the circulatory and respiratory changes produced in the normal animal by deprivation of oxygen do not occur in animals whose suprarenal capsules have been removed a few hours previously. Oliver and Schäfer, as the result of their experiments, deny the correctness of each of these statements. They believe that the results obtained by Cybulski (second statement) were due to the remaining presence of shock from the operation. An important observation by Cybulski is that the blood of the suprarenal vein contains a notable amount of the toxic principle of the gland.

Toxic doses of the extract cause, in the frog, progressively increasing loss of power without a true paralysis, and death apparently through an asthenic failure of respiration; in mammals a rapid and extreme enfeeblement, with failure of respiration and also of the circulation, consciousness being preserved very late in the poisoning. The death is apparently by asthenic failure of respiration, though when this function is artificially maintained there is finally loss of heart-power, with paralysis of the vagi nerve (Gourfein). No lesion except pulmonary congestion has been discovered after death. Gourfein, Oliver, and Schäfer find that the nerve-trunks and muscles preserve their activity to the end, so that the loss of power is not of peripheral origin.

It is evident that in the present state of our knowledge the only use of the suprarenal capsules in medicine which can be considered to rest upon the foundation of scientific rationalism is in Addison's disease. If, however, as is probable, Oliver and Schäfer are correct in their physiological conclusion, that some principle produced by the suprarenal capsule is the most powerful local known substance as a stimulant to the muscle-walls of the arterioles, it is possible that future experience may show that the suggestions of Dr. Oliver have practical value. These suggestions are that the suprarenal capsules will be useful in all forms of asthenia and anæmia in which there is very great loss of the general vasomotor tone. It is also claimed by Dr. Oliver that in anæmia there is sometimes a sharp rise in the percentage of hæmoglobin during suprarenal treatment, although it seems as yet entirely uncertain whether this ever occurs in those fatal anæmias which are grouped under the name of pernicious anæmias. The profound anæmia of Addison's disease would, however, seem to indicate that possibly the suprarenal capsules may have some relations with the blood-making organs. Dr. Oliver's trials with it in diabetes mellitus and diabetes insipidus do not appear to me to indicate that the drug has any value in these affections.

It is clear, also, that Addison's disease, so-called, is not probably a single disease, but a group of diseases. Cancerous destruction of the suprarenal capsule may well lead to the same symptoms, so far as the general system is concerned, as does tuberculous destruction of the glands. In any individual case of Addison's disease, therefore, the ultimate value of the treatment must depend upon the nature of the suprarenal lesion, whether it be one capable of invading the surrounding region and finally killing entirely, independently of any function of the suprarenal; or whether it be the expression of a widespread systemic vice, which shall manifest itself by-and-by in other parts of the body; or whether it be a simple change in the glands themselves, like a sclerosis, local in its character, of no significance save only as it affects the functions of the gland. It is plain that the suprarenal treatment of Addison's disease only supplies the loss to the body of the functional activity of the glands, and that it can have no effect upon the local lesion in the gland or upon a systemic vice which has produced that local lesion.

In regard to the dosage and method of administration it should be noted that the suprarenal gland appears to be a very active body. According to Oliver, it loses about four-fifths of its weight in drying, so that the so-called "extracts of dried gland" represent five times its weight of the fresh gland. Oliver and Schäfer found that of this extract 0.0037 gramme would produce the maximum effect in elevating the arterial pressure in a dog weighing 10 kilogrammes. In my case a glycerin extract, representing 40 grains of the gland to the fluidrachm, was used hypodermatically once a day, in doses of 10 to 15 minims; and later in dose of 20 minims by the stomach. Oliver puts the dose of the extract as 3 to 5 grains, preferably given in tabular form three times a day.

So far we have no knowledge of any systemic condition produced by exhibiting the gland freely, parallel to thyroidism which is interesting in the face of the fact that Oliver has given 120 grains of the dried (600 grains of the fresh) gland daily for a week. The suprarenal capsules are so apt to be imbedded in fat, and so hard to find, that one is inclined to doubt whether Oliver's extract was made from the pure gland. Certainly always, in making the extract, great care should be taken to see that the capsules are themselves used, and well cleansed before using.

SPLEEN. The enlargement of the spleen which occurs in myxœdema, cretinism, and after excision of the thyroid body, naturally suggests that there is a relation between the two organs, although we have no light as to the nature of the relation and whether the splenic enlargement is due to an attempt at functional replacement of the exsected or diseased thyroid, or whether it is the outcome of irritation by the presence of materials in the blood which should have been removed by the thyroid gland; or, indeed, whether it be not the result of an irritation produced by the absence of some principle made in the thyroid whose presence is necessary to the healthful life of the spleen. I am not aware that there has been any investigation as to the result of feeding the lower animals exclusively upon spleens; but the discovery of Oliver and Schäfer that the intravenous injection of the splenic extract into the dog causes an immediate fall of the arterial pressure, followed by a pronounced and continuing rise, shows that the extract is not an inert body. In a case of severe chronic exophthalmic goitre which was under my care some years ago an acute splenitis developed in a manner which was altogether inexplicable; no cause for the attack could be made out. Deep in the parenchyma of the organ there was formed an abscess whose opening and discharge were, after many months of severe sepsis and desperate illness, followed by return to health. In the second or third week of the splenitis the enlarged thyroid began to diminish, and in a short time regained the normal size. The result was a permanent cure of the exophthalmic goitre, no symptoms of the disease returning.

This case, and the reflections it gave rise to, led me to try the splenic extract in various cases of exophthalmic goitre. I have found that two practical difficulties attend its administration. If it be given by the mouth in sufficiently large doses to produce effect, it is very apt to derange violently the digestion and to cause much pain, nausea, and even vomiting; effects which, considering the small amount of material taken, are marked evidences that it is not an inert body. If the splenic extract be given hypodermatically, it very frequently causes great local irritation and even abscesses.

Obviously, it is somewhat difficult to get patients who are not under complete control to make thorough trial of splenic medication. In my dispensary service in the University of Pennsylvania in some cases there has been a distinct amelioration of the exophthalmic goitre under the influence of the remedy, but in the majority of cases the results have not been satisfactory; and in no case, so far as I know, has a cure been obtained. In these people, however, the home surroundings and circumstances are usually so inimical that any treatment has to be carried out in the face of all obstacles. Moreover, it is impossible to know whether a disagreeable, more or less repulsive medicine is taken regularly. In the University Hospital I have had one case in which, after some weeks of treatment, the patient insisted that she had entirely recovered and refused to stay longer, although there was still some remaining enlargement of the thyroid. In the case of Mrs. ——, in private practice, the disease was of six years' duration; the exophthalmus was very pronounced; the action of the heart so extremely rapid and irregular that it was almost impossible to count the pulse, which was noted, however, as being about 180. The enlargement of the thyroid was very great. The breathlessness was marked, and the general nervous erethism such that the woman was on the verge of insanity. To this patient was given by the mouth immediately a teaspoonful of the glycerin extract of spleen, made in the ordinary manner; it produced at once violent gastric distress accompanied with local pain radiating from the stomach, lasting for some hours, and followed by complete disgust for food. After a few days the dose was again exhibited, and later again, each time with similar result. Following this 10 minims were injected twice a day hypodermatically into different portions of the body; they produced much local pain and hardening of tissue, but in no case was there finally abscess; whenever the local symptoms would get intolerable the injections were temporarily stopped for a few days, small doses of the extract being given by the mouth. This was kept up for six months, when 10 drops of the spleen-extract with 10 drops of digitalis were administered three times a day. (It should be noted that early in the case digitalis and all the ordinary treatment for exophthalmic goitre had been tried without result.)

The improvement in this case began not a great while after the commencement of the hypodermatic injections, and has continued, so that today the enlargement of the thyroid gland has entirely disappeared. The general nervousness has also gone, so that the patient is hardly more neurotic than before the attack. The exophthalmus is less, though still apparent, and the cardiac action greatly reduced, though the heart remains irritable on excitement. Before the treatment the breathlessness was so extreme that the patient was not able to walk in the street at all; now she walks comfortably for a long distance, provided there be no attempt at a very brisk pace.

In the course of thirty-five years of practice I have seen a great many cases of exophthalmic goitre, and, though I have frequently witnessed relief as the result of prolonged rest and residence by the sea-shore, I have never before seen a case in which the thyroid body greatly diminished. All the usual remedies, drugs, galvanism, etc., have in my hands proved remarkably ineffectual, so that the results reached in the two cases here narrated seem to me sufficient to demand very careful, persistent trial of the splenic extract in exophthalmic goitre.

In using the extract of any of the ductless glands it must always be remembered that, if any good is achieved, it is probably the result of an addition of certain substances to the body which are normally formed in the body in sufficient quantity for its needs, but which, through accident or disease, the system has failed to supply itself with. It follows that there are usually two stages in the treatment of such a case; the first, in which the material must be given largely to put an end to the results of its long-continued absence; the second, in which the substance must be given in small doses to maintain the balance of function which has been restored. Thus, in myxœdema for the first months or years thyroid extract should be given in as large a dose as the patient can bear it; afterward, when the myxœdematous condition has subsided, the gland must be given continually in small doses, probably during the whole life.

UNIVERSITY OF PENNSYLVANIA, March 31, 1897.

THE SURGICAL TREATMENT OF APPENDICITIS.[1]

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IN studying the statistics of these sixty-nine cases it should be borne in mind that the majority of the patients were brought to the hospital by ambulance, many of them being desperately ill. As a rule, the ambulance was summoned as a last resort, after medical treatment had been employed for days or even weeks; indeed, several of the patients were sent to the hospital by their friends merely for purposes of euthanasia. With the exception of the chronic relapsing and recurrent cases, most of them were in an unfavorable state for surgical interference. This may be in part explained by the length of time intervening between the beginning of the symptoms and their arrival at the

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[1] A paper based upon the sixty-nine cases of appendicitis admitted to Dr. McCosh's service in the Presbyterian Hospital during the two years from January 1, 1895, to January 1, 1897.